REMARKS

Applicant respectfully requests reconsideration. Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are pending in this application. Claim 28 is amended. No new matter has been added.

Withdrawn Rejections

Applicants acknowledge and thank the examiner for the indication that prior rejections made on the grounds of double patenting and failure to comply with the written description have been withdrawn.

Rejection Under 35 U.S.C. 112

Claims 28, 31-33, 35, 37, 39, 40 and 42-47 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Office continues to maintain that the pending claims are not enabled because the scope of the invention is very broad and because it would require undue experimentation to practice the invention as claimed (Office Action pages 11-12). The Office also asserts that "[t]he specification at the time of filing does not correlate the immune responses generated by administering an oligonucleotide" and that "mere immune response does not predict the efficacy of the instant oligonucleotide". Applicant respectfully traverses the rejection.

In particular, the Office has objected to the inclusion of "prevention" within the scope of the claim. In order to advance prosecution Applicant has amended the claim to remove reference to the term "prevention".

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) which when administered to a subject result in aspects of the immune response being altered, along with changes in cytokine levels that are useful in the treatment of diseases such as cancer and infectious diseases. This class of oligonucleotides is described throughout the specification and the ability of these oligonucleotides to produce an immune response is not only described but data is presented in vitro and in vivo using a number of different CpG containing oligonucleotides. The data presented in the application, including that

represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3 and Example 4), and production of IL-6 (Example 8) as well as other cytokines (IFN-gamma and IL-12. Accordingly, one aspect of the invention involves the use of synthetic oligonucleotides containing CpG motifs to induce a pattern of immune response, which at the time of filing the application was recognized as being capable of causing reductions in tumors and infections.

The Office has alleged that there is no correlation between the immune responses generated according the data in the specification and the treatment of cancer, bacterial or viral infection. (Office Action page 8-9). However, as stated in the last response to Office Action, Applicant has presented several references, which were published prior to or around the priority date of the instant application. These references were presented to the Office to establish the state of the art with respect to immune system activation and the treatment of cancer at the time of filing the instant application. The references demonstrate that induction of IL-12, IFN-γ, IL-6 as well as NK cell activation is effective in the treatment of cancer. Accordingly, one of skill in the art would have recognized the utility of a CpG containing oligonucleotide which is effective in inducing IL-12, IFN-γ and NK cell activation in a method of treating cancer and infectious disease in a subject.

A review article by Trinchieri et al. (Blood, V.84, December 15, 1994, p. 4008) describes IL-12 in the production of cytotoxic lymphocytes. The role of IL-12 in antitumor immunity is discussed at length on pages 4021-4022 of the article. Studies conducted using transplantable tumors in experimental animals and showing a drastic effect of IL-12 in decreasing tumor growth and metastasis formation have been described. The Office alleges that the portion of Trinchieri et al. cited is drawn to the work of Brunda et al. (Journal Leukocyte Biology, V.55, February 1994) which teaches that "future clinical trials with this cytokine will determine if the activity demonstrated in animals can be translated into efficacy against human malignancies." The Examiner acknowledges and Applicant agrees that Brunda et al. teaches that IL-12 has potent antitumor and anti-metastatic activities in several murine tumor models (Office Action page 9). The fact that Brunda et al. mentions that future studies need to be conducted in humans is irrelevant to

the finding of IL-12 as a cytokine that has potent antitumor and antimetastatic activity in several murine tumor models. According to the MPEP, there should be no burden on the Applicant to present *in vivo* evidence in order to overcome the enablement rejection. "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." MPEP Section 2107.03.

The Office further alleges that neither Brunda et al. nor Trinchieri et al. discloses treatment with CpG oligonucleotides. The Office has also stated that U.S. Patent No. 4,883,662 issued on November 28, 1989 to Stout et al. and Hiyashi et al. (Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205) do not teach the administration of CpG oligonucleotides. As discussed above, these references were submitted to the Office in an effort to describe the state of the art at the time of filing the instant application with respect to immune responses and treatment of cancer. The references demonstrate that one of skill in the art would have recognized the utility of IL-12, IFN-γ, IL-6 as well as NK cell activation in the treatment of cancer. These references were not meant to disclose treatment with CpG oligonucleotides.

U.S. Patent No. 4,883,662 describes an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells (abstract). In the summary of the invention it is taught that "it has been established that increasing such natural killer cells is an important component of the immune system, and that accordingly the present method should be a decided advantage in cancer treatment."

The abstract of Hiyashi et al. teaches that immunotherapy with BCG-CWS results in IFN-γ induction. It is further taught that cancer patients experiencing IFN-γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN-γ induction, who died after a short period. The Office states that not all patients were able to produce IFN-γ in response to BCG cell wall. In order to overcome an enablement rejection, there is no burden on the Applicant to prove that each and every patient responds to the treatment method. According to the MPEP Section 2164.05, the evidence provided by applicant need not be conclusive but merely convincing to one of skill in the art. In view of the data in the specification the skilled artisan would have expected that CpG containing oligonucleotides would have the ability to provoke an immune

response. Although some oligonucleotides may work better than others, it is expected that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.

The Office has dismissed the teachings of Morris et al. (Infection and Immunity, 1982, 35(2):533-536), Baumgarth et al. (Journal of Virology, 1994, 68(11):7575-7581), Woodworth and Simpson (Am. J Path., vol 142 (5): 1544-55 (1993), Schneider (Genitourin. Med., 1993, vol 69 (3): 165-73), and Morris et al (Br J Obstet Gynecol, 1983, vol 90(5):412-20) stating that these references do not disclose the induction of an immune response to CpG oligonucleotides. These references were not cited by Applicant to demonstrate the ability of CpG oligonucleotides to induce an immune response, but rather to show that induction of specific cytokines was useful in the treatment of cancers and infections. Thus, one skilled in the art would recognize that a drug useful for boosting such cytokines would be useful in the treatment of viral infection. Morris et al. showed that IFNγ is produced from two human T-lymphoblastoid lines upon virus infection (see page 536, left column). Baumgarth et al. disclose that IFNγ has been identified as a key factor in immune responses to viral infections and demonstrated IFNγ production in response to influenza virus. Woodworth and Simpson employed HPV-infected and non-infected cells and analyzed their lymphokine secretion profiles. The authors report that while normal cervical cells constitutively secreted IL-1 alpha, IL-1 beta, IL-1 RA, IL-6, IL-8, TNF-alpha, and GM-CSF, the HPV-infected cell lines "exhibited significant down-regulation of IL-1 beta, IL-6, TNF-alpha, IL-8, and GM-CSF" (page 1548, right column, 1st paragraph, Figure 3, and Table 1). The authors note in their discussion that "if the constitutive release of lymphokines is involved in maintaining normal immunocompetence in the cervical mucosa, then decreased secretion might provide a more favorable environment for persistence of HPV-infected cells" (page 1552, right column, 2nd paragraph). In the abstract of Schneider, it is stated that the impaired cellular immune response upon genital HPV infection is characterized by depletion of T helper/inducer cells and/or Langerhans cells and impaired function of natural killer cells and/or the infected keratinocytes. Morris et al. studied wart virus infections with no evidence of cervical intraepithelial neoplasia and noted "a patchy reduction or total absence of Langerhans' cells in the epithelium" (page 415, left column, 2nd paragraph). Langerhans' cells are antigen-presenting cells derived from monocytes. There was also a "striking reduction in the number of T lymphocytes". Thus, one of ordinary skill

in the art would recognize the therapeutic value of CpG in treating a viral infection such as papilloma virus infection.

The teachings with respect to Sfondiri et al. and Krieg et al. have been dismissed and it is alleged that these are limited to only one type of cancer in a murine subject and that it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 activation in humans. The post-filing references were not presented to demonstrate that every CpG oligonucleotide has been used in humans to treat cancer and infectious disease as a stand alone. Rather the references were presented as evidence that, as Applicant's specification set forth, CpG oligonucleotides in fact were demonstrated following the invention to be useful in treating cancers and infectious disease in a subject. The fact that one reference is limited only to a specific cancer and is in a mouse and the other is limited to one oligonucleotide in humans, doesn't diminish the evidentiary purpose of the references.

The Office further notes that the role of IL-6 in the early response to bacterial infection has been demonstrated by Liu et al. (Infection and Immunity, Oct. 1992, p. 4402-4406). According to the Office, the time of administration of the oligonucleotide is critical for the innate response to have an effect and has not been addressed by the specification. The Office also asserts that contrary to Applicant's arguments, the mere presence of the CpG dinucleotide does not predict the efficacy in treatment of any type of cancer or bacterial or viral infections and that according to Kataoka et al. (Jpn. J. Cancer Res vol. 83 p.244-247, 1992), the active oligonucleotides contained hexameric palindromic sequence structures that are essential for biological activity. The invention is directed to a class of molecules that are useful in the treatment of diseases such as cancer and infectious diseases. Applicant was the first to recognize that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length could replicate these immune activating effects of bacterial DNA. Some of these immunostimulatory oligonucleotides comprise a palindrome. Importantly, oligonucleotides such as ODN 1, 1d, 3df and 3Md do not contain a palindrome and yet are immunostimulatory. The data provided in the specification is evidence that immunostimulatory activity results from the CpG motif, regardless of whether or not the motif is present in a palindrome. The fact that the art suggests that some oligonucleotides may work better

than others is not sufficient to contradict the teaching that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.

One of skill in the art would have recognized that the pattern of immune response elicited by these oligonucleotides would be useful in the treatment of cancer and infectious disease. Data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. Furthermore, a number of clinical trials involving administration of bacterial DNA to humans showed positive effects in various cancer patients (Tokunaga et al Jpn. J. Infect. Dis 52, 1-11, 1999), thereby confirming the utility of the CpG oligonucleotides in the treatment of cancer.

In conclusion, a consideration of the Wands factors in their entirety including the teachings in the specification, the in vitro and in vivo working examples demonstrating immunostimulation by CpG oligonucleotides, the level of ordinary skill and the state of the art at the time of filing evidences that one of ordinary skill in the art would have been able to make and use the claimed invention without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

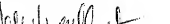
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US06.

Dated: July 13, 2009

Respectfully submitted,

By 

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000